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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/538,231	11/25/2005	Ofer Mandelboim	2488.019	8744

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EXAMINER
DAVIS, MINH TAM B

ART UNIT	PAPER NUMBER
1642	

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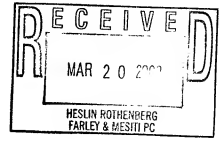
Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.



Office Action Summary	Application No.	Applicant(s)	
	10/538,231	MANDELBOIM ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-44* is/are pending in the application.

4a) Of the above claim(s) *6-18 and 24-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 19-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *02/21/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election without traverse of group I, claims 1-5, 19-23, SEQ ID NO:4, species immunoglobulin, in the response of 01/28/08 is acknowledged.

Accordingly, group I, claims 1-5, 19-23, SEQ ID NO:4, species immunoglobulin, are examined in the instant application.

The embodiment of claims 1-5, 19-23, as drawn to the species a conjugate of NKp30 and a cytotoxic agent has been withdrawn from consideration as being drawn to non-elected invention. Claims 6-18, 24-44 have been withdrawn from consideration as being drawn to non-elected invention.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5, 19-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Claims 1-5, 19-23 are indefinite for the use of the language "active fragment" in claims 1, 19. It is not clear what type of activity is referred to.

2. Claim 5 is indefinite, because it is not clear what type of function is referred to.

Claim Rejections - 35 USC § 112, First Paragraph, Scope

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 19-23 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a conjugate of NKp30 or a fragment thereof that binds to a target tumor cell and an immunoglobulin or its Fc fragment, does not reasonably provide enablement for a conjugate of NKp30 or a functional fragment thereof that binds to "a cellular ligand" expressed on the surface of a target tumor cell, and "a fragment of an immunoglobulin". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

To comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, the specification must enable one skilled in the art to make and use the claimed invention without undue experimentation. The claims are evaluated for enablement based on the Wands analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731,8 USPQ2d 1400 (Fed.Circ.1988) as follows: (1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.

The specification discloses that a conjugate of the extracellular portion of a natural killer cell receptor NKp30 and the constant region of a human IgG1 heavy chain (p.27, last paragraph) binds to an **unknown ligand** on PC3 prostate cancer cell line, and mediates lysis of the target cancer cell via macrophage-dependent lysis mechanism (Example 2 on page 30). The specification discloses that said conjugate inhibits growth of PC-3 cells inoculated s.c. in mice (Example 3 on page 30).

As written, claims 1-5, 19-23 encompass a conjugate of NKp30 and any fragment of an immunoglobulin, that binds to any cellular ligand expressed on the surface of a target tumor cell.

One cannot predict which molecule on cancer cell surface is the ligand for NKp30, because as admitted by the specification, NKp30-Ig conjugate binds to an unknown ligand on the surface of PC3 prostate cancer cell line.

Further, one cannot predict that any fragment of an immunoglobulin exerts a cytotoxic effect on the target cell, because a fragment of an immunoglobulin could be as small as a two amino acids. Which fragment is not predictably capable of mediate macrophage-dependent lysis, as disclosed for NKp30-Fc conjugate.

Given the above unpredictability, and in view of the complex nature of the invention, a lack of sufficient disclosure in the specification, and little is known in the art concerning the claimed invention, there would be an undue quantity of experimentation required for one of skill in the art to practice the claimed invention, that is commensurate in scope of the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

A. Claims 1-4 are rejected under 35 U.S.C. 102(a) as being anticipated by WO 02/08287 A2 (Mandelboim et al, January 31, 2002, IDS of 02/13/06).

Claims 1-4 are as follows:

1. A polypeptide conjugate comprising: (a) a target recognition segment comprising a Natural Killer cell receptor (NCR) or an active fragment thereof, wherein the NCR is selected from the group consisting of: NKp30 or a functional fragment thereof that binds to a cellular ligand expressed on the surface of a target tumor cell; and (b) a second segment comprising an active agent capable of exerting a cytotoxic effect on the target cell.

2. The conjugate according to claim 1, wherein the active agent is an immunoglobulin (Ig) molecule or a fragment thereof.

3. The conjugate according to claim 2, wherein the active agent is the Fc fragment of the immunoglobulin molecule.

4. The conjugate according to claim 3, wherein the conjugate comprises NKp30 covalently attached to the Fc fragment of an Ig molecule.

WO 02/08287 A2 teaches a conjugate of NKp30 and an immunoglobulin or its fragment, an Fc fragment (p.61 and claims 1, 8).

B. Claims 1-2 are rejected under 35 U.S.C. 102(b) as being anticipated by Pende et al, 1999 (J Exp Med, 190(10): 1505-1516, IDS of 02/13/06).

Claims 1-2 are as follows:

1. A polypeptide conjugate comprising: (a) a target recognition segment comprising a Natural Killer cell receptor (NCR) or an active fragment thereof, wherein the NCR is selected from the group consisting of: NKp30 or a functional fragment thereof that binds to a cellular ligand expressed on the surface of a target tumor cell; and (b) a second segment comprising an active agent capable of exerting a cytotoxic effect on the target cell.

2. The conjugate according to claim 1, wherein the active agent is an immunoglobulin (Ig) molecule or a fragment thereof.

Pende et al teach that addition of a full length antibody, that cross-links NKp30, induces NK cytolytic activity (p.1509, second column, third paragraph).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

A. Claims 1-5 are rejected under 35 U.S.C. 103(a) as being obvious over Pende et al, 1999 (J Exp Med, 190(10): 1505-1516, IDS of 02/13/06), in view of Mandelboim et al, Nature, February 2001, 409: 1055-1060.

Claims 1-5 are as follows:

1. A polypeptide conjugate comprising: (a) a target recognition segment comprising a Natural Killer cell receptor (NCR) or an active fragment thereof, wherein the NCR is selected from the group consisting of: NKp30 or a functional fragment thereof that binds to a cellular ligand expressed on the surface of a target tumor cell; and (b) a second segment comprising an active agent capable of exerting a cytotoxic effect on the target cell.

2. The conjugate according to claim 1, wherein the active agent is an immunoglobulin (Ig) molecule or a fragment thereof.

3. The conjugate according to claim 2, wherein the active agent is the Fc fragment of the immunoglobulin molecule.

4. The conjugate according to claim 3, wherein the conjugate comprises NKp30 covalently attached to the Fc fragment of an Ig molecule.

5. The conjugate according to claim 4, having the amino acid sequence as set forth in SEQ ID NO:4 or functional fragments thereof.

It is noted that SEQ ID NO:4 is composed of a leader peptide of CD5, a KpnI restriction site, NKp30 and an Fc region (specification, p.23).

Pende et al teach the structure of NKp30 protein and its encoding cDNA sequence, having a signal peptide and an extracellular region (p.1512, first column, figure 7B on page 1512). Pende et al teach that NKp30 is receptor expressed by natural killer (NK) cells (abstract). Pende et al teach that NKp30, and not NKp46 or NKp44, is the major receptor involved in NK-mediated lysis of certain tumors (abstract, p.1514, first column, first paragraph). Pende et al teach that NKp30 is the third member of the family of Natural killer cell receptors (NCR), comprising NKp46 and NKp44 (p.1514, second column, second paragraph). Pende et al teach that similar to NKp46, NKp30 is expressed by all NK cells, involved in NK cell activation and target cell killing by fresh NK cells (p.1513-1514, items under Discussion). Pende et al teach that addition of a full length antibody, that cross-links NKp30, but not by its F(ab')2 fragment, induces NK cytolytic activity (p.1509, second column, third paragraph). Pende et al teach that mAb-dependent NKp30 stimulation requires efficient cross-linking mediated by the Fc receptor on target cells (p.1509, second column, third paragraph). It is well known in the art that F(ab')2 fragment does not have Fc fragment. Thus, from the teaching of Pende et al, it is clear that the Fc portion of an immunoglobulin molecule is required for cross-linking NKp30 and its activation, upon binding of the Fc fragment to its receptor on target cells.

Pende et al do not teach a conjugate of NKp30 and an immunoglobulin or its Fc fragment.

Mandelboim et al, 2001, teach that a soluble conjugate of an extracellular region of NKp46 and Fc region of an immunoglobulin recognizes haemagglutinins on virus-infected cells, and activates lysis by human NK cells (abstract, p.1055).

It would have been prima facia obvious to one of ordinary skill in the art at the time the invention was made to replace NKp46 in the NKp46-Fc conjugate taught by Mandelboim et al with another member of the NCR family, NKp30, for making NKp30-Fc conjugate for lysis of target cancer cells, in view that the conjugate NKp46-Fc by itself, without addition of a separate antibody, recognizes target cells, and induces lysis of target cells by NK cells, as taught by Mandelboim et al, and further in view that NKp30, but not NKp46, is the main NK receptor that lyses tumor cells, as taught by Pende et al.

Moreover, SEQ ID NO:4 or its functional fragment is obvious, in view that SEQ ID NO:4 is composed of a leader peptide of CD5, a KpnI restriction site, NKp30 and an Fc region. It would have been obvious to replace the signal peptide taught by Pende et al with a leader peptide and a restriction site for making and expressing the conjugate and for facilitating its secretion.

One would have been motivated to do so, because of the following reasons:

1) The conjugate of NKp30-Fc or NKp46-Fc would be more efficient and advantageous than a composition comprising NKp30 or NKp46 and a separate, added antibody for their activation and inducing killing of target cells, and

2) the Fc portion of the conjugate would mediate cross-linking of NKp30 upon its binding to Fc receptor on target cells, and consequently, activation of NKp30, in view of the teaching of Pende et al.

B. Claims 19-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pende et al, 1999, J Exp Med, 190(10): 1505-1516, IDS of 02/13/06, in view of Mandelboim et al, Nature, February 2001, 409: 1055-1060 as applied to claims 1-5 above, and further in view of Sukhatme et al (US 6,797,488).

Claims 19-23 are as follows:

19. A pharmaceutical composition comprising as an active ingredient a polypeptide conjugate comprising:

(a) a target recognition segment comprising an NCR or an active fragment thereof, the NCR selected from the group consisting of: NKp30, or a functional fragment thereof, that binds to a cellular ligand expressed on the surface of a target tumor cell; and

(b) a second segment comprising an active agent that promotes the lysis of the target tumor cell; and (c) a pharmaceutically acceptable carrier, stabilizer or diluent.

20. The pharmaceutical composition according to claim 19, wherein the active agent is an immunoglobulin (Ig) molecule, or a fragment thereof.

21. The pharmaceutical composition according to claim 20, wherein the active agent is the Fc fragment of the immunoglobulin molecule.

22. The pharmaceutical composition according to claim 19, wherein the conjugate comprises NKp30 covalently attached to the Fc fragment of an Ig molecule.

Claims 19-23 recite the claimed conjugate, formulated as a pharmaceutical composition. However, this limitation is viewed as a recitation of intended use and therefore is not given patentable weight in comparing the claims with the prior art. Claims 19-23 read on the ingredient per se, which is a conjugate of NKp30 and an immunoglobulin or a fragment thereof.

The teaching of Pende et al and Mandelboim et al has been set forth above.

Pende et al and Mandelboim et al do not teach a pharmaceutically acceptable carrier.

Sukhatme et al (US 6,797,488) teach an anti-angiogenic protein, fusion protein thereof (column 2, item under Summary of the invention, bridging column 3), and a composition thereof, wherein the protein is combined with a pharmaceutically acceptable carrier (column 16, last paragraph, bridging column 17).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the conjugate taught by a pharmaceutically acceptable carrier with a pharmaceutically acceptable carrier, as taught by Sukhatme et al, for its storage.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, LARRY HELMS can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MINH TAM DAVIS
March 08, 2008

/Larry R. Helms/

Supervisory Patent Examiner, Art Unit 1643

Notice of References Cited	Application/Control No. 10/538,231	Applicant(s)/Patent Under Reexamination MANDELBOIM ET AL.	
	Examiner MINH-TAM DAVIS	Art Unit 1642	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-6,797,488	09-2004	Sukhatme, Vikas P.	435/69.1
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Mandelboim et al, Nature, February 2001, 409: 1055-1060.
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.